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Epidemiology of twinning in the National Birth Defects Prevention Study, 1997–2007

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Abstract

Background—Our objective was to evaluate associations between twinning and maternal demographic factors and periconceptional exposures among infants with and without orofacial clefts.

Methods—We used data from the National Birth Defects Prevention Study; 228 twins and 8,242 singletons without birth defects (controls), and 117 twins and 2,859 singletons with orofacial clefts, born 1997–2007, were included in the analyses. Because of the occurrence of twinning due to the use of assisted reproductive technologies, logistic regression models were computed to estimate odds ratios (OR) and 95% confidence intervals (CIs) for each exposure, stratified by fertility treatment use. To evaluate factors by zygosity, we used sex-pairing data and a simulation approach to estimate the zygosity of like-sex twin pairs for unassisted conceptions.

Results—Among control mothers who did not use fertility treatments, predictors of twinning included non-Hispanic black maternal race (adjusted OR: 1.6, 95% CI: 1.0–2.4), and tobacco smoking (1.6, 1.1–2.4). Among control mothers who used fertility treatments, older maternal age, higher income, and state of residence were associated with twinning. Associations were generally stronger among mothers of dizygotic (estimated) twins than monozygotic (estimated) twins. Results for mothers of infants with isolated orofacial clefts were similar to those of controls.

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Conclusion—We observed an increased twinning frequency with increasing maternal age, but factors such as maternal race/ethnicity and socioeconomic status may also contribute. Among women receiving fertility treatments, factors associated with twinning suggested a relation with treatment specifics (e.g., treatment type and number of embryos implanted) and availability of insurance coverage.

Keywords

twinning; ART; IVF; orofacial clefts; clomiphene citrate

INTRODUCTION

In 2011, one in every 30 babies born in the United States was a twin (Martin et al., 2013). Twinning is associated with a number of pregnancy complications and adverse maternal and fetal outcomes (Helmerhorst et al., 2004; Boulet et al., 2008; Morcel et al., 2010; Yang et al., 2011). Mothers of multiples have twice the risk of pregnancy-related mortality and an increased risk of preterm labor and cesarean delivery (Conde-Agudelo et al., 2000). Compared to singletons, twins are at a higher risk of low birth weight, birth defects, prematurity, and infant mortality (Martin and Park, 1999; Li et al., 2003a; Tang et al., 2006; Chauhan et al., 2010; Zhang et al., 2011). The increased risk for adverse outcomes is particularly concerning given the increasing rate of twin births in the United States from 1980 (18.9 per 1000) to 2011 (33.2 per 1000) (Martin et al., 2013).

Recent studies have estimated that approximately 19% of US twin births are attributable to assisted reproductive technology (ART) and an additional 19% of twin births are attributable to non-ART ovulation stimulation treatments (Sunderam et al., 2012; Kulkarni et al., 2013). Other factors that are associated with twinning include a family history of twinning, older maternal age, multiparity, obesity, and African-American race (Khoury and Erickson, 1983; Allen and Parisi, 1990; Martin and Park, 1999; Hoekstra et al., 2010). The relationships between twinning and oral contraceptives, folic acid-containing multivitamins, and maternal smoking have been examined, with conflicting results (Rothman, 1977; Olsen et al., 1988; Czeizel et al., 1994; Li et al., 2003b; Muggli and Halliday, 2007; Hoekstra et al., 2010).

Although twinning has been studied extensively, much of the work involving risk factors for twinning was conducted before fertility treatments were in widespread use. Given the steady increase in use of assisted reproduction, understanding the factors associated with multiple births in this population is important (Centers for Disease Control and Prevention et al., 2011). In addition, few studies have evaluated factors associated with twinning among mothers whose offspring have birth defects (Tang et al., 2006; Zhang et al., 2011). Our objectives were to use data from the National Birth Defects Prevention Study (NBDPS) to evaluate maternal demographic factors and periconceptional exposures associated with twinning, stratified by use of fertility treatments. We assessed these associations among mothers of unaffected controls. We also included mothers of infants or fetuses with a birth defect (cases) so that we might compare these findings with those of control mothers. Because twinning is associated with an increased risk of birth defects, we were interested in factors associated with twinning that were unique to the case group, as we hypothesized that these factors may be related to both the birth defect and twinning. In order to minimize heterogeneity, we selected one phenotype - isolated cleft lip with/without cleft palate or cleft palate only (cases) - as these are some of the more common birth defects that have previously been associated with twinning (Mastroiacovo et al., 1999; Tang et al., 2006; Zhang et al., 2011).

MATERIALS AND METHODS

Study Population

The NBDPS was a multi-center case-control study of major birth defects in the United States that completed data collection in 2013. NBDPS is a collaborative effort of the Centers for Birth Defects Research and Prevention in Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah. Institutional Review Boards at each site approved the study. Methods for recruitment of participants and data collection have been described in detail (Yoon et al., 2001; Rasmussen et al., 2003). Briefly, eligible cases included infants or fetuses with major birth defects identified through population-based surveillance systems at each site. Controls, live-born infants without major birth defects, were randomly selected using birth certificates or birth hospital records from the same ascertainment area and time period as the cases. Per study protocol, only one infant per family was eligible for NBDPS participation; when both twins met inclusion criteria, the first-born twin was included.

Mothers of cases and controls participated in a computer-assisted telephone interview, which included questions regarding pregnancy history, demographics, and exposures that occurred from three months before conception through the end of the pregnancy. Mothers were interviewed in English or Spanish between six weeks and 24 months after their expected date of delivery (EDD).

Our study population included mothers of control twins (n=228) and singletons (n=8,242), and mothers of case twins (n=117) and singletons (n=2,859) with EDD between October 1, 1997 and December 31, 2007. Mothers of higher order multiples were excluded. Clinical information was reviewed by a clinical geneticist (SAR) to identify cases with isolated clefts (no additional unrelated major defect and no known genetic conditions) (Rasmussen et al., 2003).

Outcome

The outcome of interest for this analysis was twin pregnancy, as compared to singleton pregnancy. During the interview, mothers were asked, “In this pregnancy, how many babies were you carrying?” If necessary, a second question was asked, “Did you have a single baby, twins, or more babies?” Secondary sources of plurality information were birth certificates and/or maternal medical records. Mothers of 17 controls and five cases did not answer the plurality question, but clinical records indicated they were singletons. Approximately 18% of maternally reported twin control infants (n=41/228) and twin cases (n=21/117) were reported as singletons on the birth certificate. This could be due to clerical errors or to death of a co-twin *in utero*. Therefore, we elected to defer to the maternal interview response. All infants reported as singletons during the interview were also identified as singletons on birth certificates. One control mother was excluded due to missing information on plurality in both information sources.

Exposure

We examined the association between twinning and maternal characteristics that were previously reported to be associated with twinning including fertility treatments, race/ethnicity, age, height, pre-pregnancy weight, pre-pregnancy body mass index (BMI), parity, education, income, tobacco smoking, oral contraceptive use, and use of a folic acid-containing multivitamin. All exposures were self-reported by mothers. Fertility treatment was defined as any use of fertility-enhancing medications (e.g., clomiphene citrate) and/or ART (in vitro fertilization [IVF], gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, and intracytoplasmic sperm injection) and clomiphene citrate use only. Women were excluded from the analyses stratified by use of fertility treatments if they reported use of only non-medical fertility treatments (e.g., consumption of teas, use of acupuncture). As our focus was on maternal characteristics associated with twinning, mothers reporting only paternal treatments (e.g., vasectomy reversal) were also excluded.

Maternal cigarette smoking, oral contraceptives, and folic acid-containing multivitamins were assessed for the exposure window from one month before through the first month of pregnancy. In order to be consistent with previous analyses of twinning and body composition, maternal height and maternal pre-pregnancy weight were examined separately and were categorized as quartiles among mothers of singleton controls (height: < 159, 159–163, 164–168, and > 168 cm; pre-pregnancy weight: < 57, 57–64, 65–74, > 74 kg) (Basso et al., 2004; Reddy et al., 2005; Hoekstra et al., 2010). Pre-pregnancy BMI was categorized according to NIH guidelines: underweight (< 18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥ 30) (National Heart Lung and Blood Institute, 2000). Study site and year of EDD were also included as covariates.

Statistical Analyses

Logistic regression analyses were used to estimate crude odds ratios (ORs) and corresponding 95% confidence intervals (CI). Models were also stratified by fertility treatment, comparing maternal fertility use to unassisted conception. In the analyses of mothers who reported unassisted conceptions, we calculated adjusted estimates using multivariable logistic regression, controlling for covariates selected *a priori* using causal diagrams, also known as directed acyclic graphs (Greenland et al., 1999).

Previous studies have shown that predictors of twinning may vary depending on zygosity (Basso et al., 2004; Hankins and Saade, 2005; Hoekstra et al., 2010). The NBDPS does not routinely collect information on zygosity or sex of the co-twin. Therefore, the sex of many of the co-twins was obtained through linkage with birth certificates utilizing maternal name, infant name, and infant date of birth to merge records. The co-twin's sex for 176 of 228 control twin pairs (77.2%) was identified: 60 male-male pairs, 52 female-female pairs, and 64 male-female pairs. These data were not available for Utah participants; therefore the twin (n=17) and singleton (n=591) controls from this Center were excluded from the zygosity sub-analysis. Due to small sample size, the zygosity sub-analysis was not conducted for case twins among which there were 49 (60.5%) same sex pairs, and 32 (39.5%) unlike sex pairs.

Unlike-sex twin pairs are dizygotic, but the zygosity of like-sex pairs cannot be identified without further information. To estimate the zygosity of like-sex pairs, we utilized a simulation modeling approach. The steps in this approach were: calculate the proportion of male twins in our sample, estimate the proportion of DZ twins among control twins, estimate the proportion of MZ twins among the like-sex twins in our sample, simulate 1,000 datasets with zygosity randomly assigned to each like-sex twin pair, estimate ORs for each factor of interest in each dataset using logistic regression, and, finally, obtain summary ORs and 95% uncertainty intervals for each factor of interest (see Appendix). The parameters for modeling zygosity were obtained from equations described in 2009 by Hardin et al. We also estimated ORs and 95% CIs for the association between the variables of interest and twinning for the like-sex and unlike-sex pairs as a more traditional method of accounting for zygosity. SAS version 9.3 (Cary, NC) was used to conduct all analyses.

RESULTS

Approximately 2.7% (n=228/8470) of control mothers reported a twin gestation compared to 3.9% (n=117/2976) of case mothers (i.e. fetus/infant with orofacial cleft). The interview participation rate was 68.4% for mothers of cases and 65.7% for mothers of controls. Approximately 31.1% of mothers of control twins and 29.9% of mothers of case twins reported use of fertility treatments (Table 1). Fertility treatment use was significantly associated with twinning for control mothers (OR: 14.5, 95% CI: 10.7–19.8) and case mothers (OR: 9.5, 95% CI: 6.2–14.8). ART use and clomiphene citrate use were significantly associated with twinning among control mothers (OR: 51.0, 95% CI:31.8–81.7; OR:6.1, 95% CI:3.5–10.7, respectively) and case mothers (OR:23.6, 95% CI:12.8–43.6; OR: 5.3, 95% CI:2.5–11.1, respectively).

Results were generally similar for case and control mothers (Table 1). Among control mothers, twinning increased with increasing maternal age: 58.8% of mothers of twins were age 30 years or greater, compared to 38.4% of mothers of singletons. Among control mothers, other factors significantly associated with an increased prevalence of twinning in bivariate analyses were higher education (> than a high school graduate), higher income (> $50,000 per year), and use of a folic acid-containing multivitamin. Hispanic control mothers were also less likely to have twins compared to non-Hispanic white mothers. Among mothers of cases with clefts, significant predictors of twinning were taller maternal height, higher maternal income, and use of a folic-acid containing multivitamin. A sensitivity analysis restricted to mothers who reported plurality during the interview that matched birth certificates (control twins: n=187; case twins: n=96) resulted in very similar findings (data not shown).

Several factors were found to be significantly associated with twinning among control mothers who reported unassisted conception (Table 2). For these women, the association between non-Hispanic black race and twinning was of borderline significance after adjusting for study site (adjusted odds ratio [aOR]:1.6, 95% CI: 1.0–2.4). Increasing parity was modestly associated with twinning, with ORs of borderline statistical significance after adjusting for maternal age, race/ethnicity, education level, annual household income, and study site (1 previous live birth: 1.4, 0.9–2.1; 2+ previous live births: 1.6, 1.0–2.5). Maternal tobacco smoking was significantly associated with twinning after adjusting for maternal age, race/ethnicity, education level, annual household income, parity, study site, and year of EDD (1.6, 1.1–2.4).

Among the control mothers who reported any use of fertility treatments, twinning was more frequent among mothers aged 30–34 years compared to mothers aged 25–29 years (Table 2). The proportion of non-Hispanic white mothers was slightly higher among mothers of twins (91.6%) than among mothers of singletons (83.9%). The odds of twinning were 4.3 times higher for mothers with an annual household income ≥ $50,000 compared to those with an income between $10,000 and $50,000 (95% CI: 1.9–9.9). Twinning was less common among mothers 159–163 cm tall than among mothers <159 cm tall.

Among case mothers who did not report use of fertility treatments, non-Hispanic black women were more than twice as likely as non-Hispanic white women to have a twin pregnancy (aOR 2.3, 95% CI: 1.1–4.6) (Table 3). Compared to women with no previous live births, women with at least two previous live births had a modestly increased risk of a twin pregnancy that was of borderline statistical significance (1.7; 95% CI: 0.9–3.1). Mothers from New York were also significantly more likely to have a twin pregnancy than their counterparts from Georgia, although this association was of borderline significance after adjusting for year of EDD. Overall, the associations for case mothers were similar to the findings from the controls analysis, with the notable exception that there was no association observed for smoking and twinning among case mothers reporting unassisted conception. We did not observe any significant associations with twinning among case mothers who reported use of fertility treatments, although the small sample size limited our ability to detect associations in this group.

Associations with twinning for the unlike-sex control twins and estimated dizygotic twins were similar to the associations observed for all control twins (Table 4). Fewer associations were observed for the like-sex and estimated monozygotic control twins.

DISCUSSION

Twin pregnancies occurred in approximately 2.7% of control mothers in the NBDPS, similar to the U.S. twin birth rate of 3% during the same time period (Martin et al., 2013). As expected, fertility treatment use was a significant predictor of twinning, both for mothers of controls and of cases with isolated orofacial clefts. Our results support previous reports of an association between fertility treatments and MZ twinning (Aston et al., 2008). Given the magnitude of the associations for ART and clomiphene citrate, it may appear that our results indicate a greater contribution of ART births to the overall twinning rate compared to non-ART treatments, in contrast to previous studies (Kulkarni et al., 2013). However, when comparing the proportion of twins attributable to IVF with non-IVF treatments, without adjusting for maternal age, our results (16.7% of twins and 14.5%, respectively) were similar to those of Kulkarni et al (2013). We did not find any evidence to suggest a difference in the factors associated with twinning for unaffected controls and cases with orofacial clefts.

Historically, maternal age has been cited as a strong predictor of twinning (Bulmer, 1970; Bortolus et al., 1999). A recent report found the natural dizygotic twinning rate was relatively stable between 1969–2009 after controlling for maternal age (Derom et al., 2011). We found an association between maternal age and twinning for mothers reporting assisted conception but not among mothers reporting unassisted conception. One explanation for the discrepancy may be that we could not account for zygosity in our primary analyses, and previous studies have suggested that the association with maternal age may be limited to mothers of DZ twins (Bulmer, 1970). In our zygosity sub-analysis we observed a trend of increased frequency of twinning with increasing maternal age for MZ and DZ twins, although the association was not statistically significant for MZ twin mothers. Our finding that the association between maternal age and twinning was attenuated after controlling for fertility treatment use, maternal race/ethnicity, education level, annual household income, study site and year of EDD may suggest that this association is more complex than previously described.

Other factors associated with both fertility treatments and twinning such as education, pre-pregnancy weight, and use of a folic acid-containing multivitamin were associated with twinning when not controlling for fertility treatment use but were no longer associated after the models were stratified by fertility treatment use. The possibility of an association between folic acid and twinning has been particularly controversial (Werler et al., 1997; Li et al., 2003b). Our study found little difference in folic acid intake during the pregnancies of twin and singleton mothers reporting unassisted conception. In the ART stratum, almost all mothers reported taking folic acid. Although more twin mothers reported taking folic acid, this association was not statistically significant.

Among mothers who reported unassisted conception, a moderate increase in the frequency of twinning was observed for mothers who were non-Hispanic black, who reported two or more previous live births, and who smoked cigarettes between one month prior to conception through the first month of pregnancy, which is consistent with previous findings (Bulmer, 1970; Nylander, 1981; Hoekstra et al., 2010).

The associations we observed for mothers reporting fertility treatments likely reflect the cost of fertility treatments or choices regarding treatment options, such as implanting multiple embryos, rather than causal factors. The association between income and twinning may be due to treatments such as IVF being cost-prohibitive to lower income families and many insurers do not provide coverage for these treatments (American Society for Reproductive Medicine, 2014). Cost has been previously cited as a factor related to the socioeconomic and ethnic disparities among women utilizing fertility treatments (Smith et al., 2011). Similarly, the large proportion of twin births in MA are likely due to state mandates that insurers provide coverage for fertility treatments, including IVF (Martin et al., 2011). For women receiving IVF, choices regarding the number of embryos implanted are an important consideration, although not one that we were able to analyze.

Our study has several limitations. First, our study was limited by the relatively small sample size after stratifying by fertility treatment use and estimated zygosity. We were unable to conduct multivariable analyses for mothers reporting fertility treatment use. We relied on self-reported data from a retrospective maternal interview, so we cannot rule out exposure misclassification due to inaccurate recall. The average age at interview was nine months for controls (singletons: 9.3 months; twins: 10.1 months) and 11 months for cases (singletons: 10.7 months; twins: 11.3 months). The study participation rate was slightly higher among mothers of twins than mothers of singletons for both controls (singletons: 65.4%; twins: 68.7%) and cases (singletons: 68.2%; twins: 71.6%). We were not able to verify the accuracy of the responses for reported periconceptional exposures or reported use of fertility treatments. For mothers who reported fertility treatment use, we were unable to determine the number of embryos implanted, a strong predictor of twinning (Templeton and Morris, 1998). Another limitation is that a comparison of the plurality reported by the mothers in the interview with information recorded on the infant's birth certificate or mother's hospital record revealed some discrepancies, with mothers reporting higher rates of twin gestation. Although previous studies have found a high degree of concordance between plurality from maternal report and on birth certificates, some variability exists and may be due to clerical errors or early fetal demise of a co-twin (Querec, 1980; Schoendorf et al., 1993). Ascertainment of early fetal demise has likely increased since these previous studies due to increased use of early ultrasonography. A sensitivity analysis restricted to control infants without plurality discrepancies produced results similar to those from the primary analysis.

We were also unable to directly determine zygosity. This limitation is important because many factors have only been associated with DZ twinning (Bulmer, 1970; Hoekstra et al., 2010). Zygosity is particularly difficult to obtain as the gold-standard for determining zygosity is genetic analysis (Chen et al., 1999). However, our simulation modeling approach may be useful as it allowed us to estimate risk factor associations for MZ and DZ twins with accompanying uncertainty intervals. Although we attempted to assess factors associated with zygosity of twins, there are other features of twinning, such as chorionicity, that we were not able to assess using these data.

Strengths of this study include use of a demographically diverse, population-based sample from ten different states across the United States. We were able to control for a variety of factors associated with twinning. This analysis assesses potential risk factors for twinning among a modern sample of mothers that reported fertility treatment use in addition to mothers that reported unassisted conception of twins.

Fertility treatment use was a strong predictor of twinning, as expected, but the factors associated with twinning among women receiving fertility treatments are likely due, in part, to the type of treatment, number of embryos implanted, and the availability of insurance coverage. We observed an increase in twinning with increasing maternal age, but factors such as maternal race/ethnicity and socioeconomic status may contribute and should be examined further. Given the increased risk of adverse outcomes associated with a twin pregnancy, understanding the factors associated with twinning, be it unassisted or assisted, is of public health importance.

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Table 1

Characteristics of mothers of twins and singletons, National Birth Defects Prevention Study, 1997–2007

	Controls							Isolated Orofacial Clefts						
	Mothers of twins		Mothers of singletons					Mothers of twins		Mothers of singletons				
Maternal characteristic	n	%	n	%	cOR	LCL	UCL	n	%	n	%	cOR	LCL	UCL
Total	228		8242					117		2859				
Fertility treatment use (any)														
Yes	71	31.1[a]	249	3.0	**14.5**	**10.7**	**19.8**	35	29.9	121	4.2	**9.5**	**6.2**	**14.8**
No	155	68.0	7906	95.9	Ref			82	70.1	2706	94.7	Ref		
Assisted reproductive technology use														
Yes	39	17.1	39	0.5	**51.0**	**31.8**	**81.7**	20	17.1	28	1.0	**23.6**	**12.8**	**43.6**
No	155	68.0	7906	95.9	Ref			82	70.1	2706	94.7	Ref		
Clomiphene citrate use														
Yes	15	6.6	125	1.5	**6.1**	**3.5**	**10.7**	9	7.7	56	2.0	**5.3**	**2.5**	**11.1**
No	155	68.0	7906	95.9	Ref			82	70.1	2706	94.7	Ref		
Age at delivery (years)														
<25	39	17.1	2802	34.0	**0.6**	**0.4**	**0.9**	27	23.1	992	34.7	0.7	0.4	1.1
25–29	55	24.1	2273	27.6	Ref			31	26.5	769	26.9	Ref		
30–34	79	34.7	2044	24.8	**1.6**	**1.1**	**2.3**	35	29.9	667	23.3	1.3	0.8	2.1
≥35	55	24.1	1123	13.6	**2.0**	**1.4**	**3.0**	24	20.5	431	15.1	1.4	0.8	2.4
Race/ethnicity														
Non-Hispanic white	158	69.3	4828	58.6	Ref			78	66.7	1803	63.1	Ref		
Non-Hispanic black	31	13.6	927	11.3	1.0	0.7	1.5	10	8.6	169	5.9	1.4	0.7	2.7
Hispanic	27	11.8	1944	23.6	**0.4**	**0.3**	**0.6**	22	18.8	682	23.9	0.7	0.5	1.2
Other	12	5.3	534	6.5	0.7	0.4	1.2	7	6.0	204	7.1	0.8	0.4	1.7
Height (cm)														
<159	53	23.3	2084	25.3	Ref			23	19.7	756	26.4	Ref		
159–163	56	24.6	2085	25.3	1.1	0.7	1.5	30	25.6	675	23.6	1.5	0.8	2.5
164–168	53	23.3	1874	22.7	1.1	0.8	1.6	23	19.7	644	22.5	1.2	0.7	2.1
>168	62	27.2	1881	22.8	1.3	0.9	1.9	36	30.8	666	23.3	**1.8**	**1.0**	**3.0**
Pre-pregnancy weight (kg)														

Maternal characteristic	Controls							Isolated Orofacial Clefts						
	Mothers of twins		Mothers of singletons					Mothers of twins		Mothers of singletons				
	n	%	n	%	cOR	LCL	UCL	n	%	n	%	cOR	LCL	UCL
<57	48	21.1	2060	25.0	Ref			22	18.8	720	25.2	Ref		
57–64	56	24.6	2327	28.3	1.0	0.7	1.5	31	26.5	759	26.7	1.3	0.8	2.3
65–75	66	29.0	1880	22.8	**1.5**	**1.0**	**2.2**	27	23.1	639	22.4	1.4	0.8	2.5
>75	53	23.3	1875	22.8	1.2	0.8	1.8	36	30.8	698	24.4	1.7	1.0	2.9
Pre-pregnancy body mass index (kg/m^2)														
Underweight (<18.5)	10	4.4	426	5.2	0.9	0.5	1.7	8	6.8	184	6.4	1.1	0.5	2.4
Normal (18.5–24.9)	117	51.3	4347	52.7	Ref			55	47.9	1437	50.3	Ref		
Overweight (25–29.9)	55	24.1	1794	21.8	1.1	0.8	1.6	24	20.5	598	20.9	1.0	0.6	1.7
Obese (≥ 30)	38	16.7	1317	16.0	1.1	0.7	1.6	25	21.4	506	17.7	1.3	0.8	2.1
Parity														
0	94	41.2	3286	39.9	Ref			48	41.0	1123	29.3	Ref		
1	75	32.9	2730	33.1	1.0	0.7	1.3	37	31.6	976	34.1	0.9	0.6	1.4
2+	59	25.9	2206	26.8	0.9	0.7	1.3	32	27.4	751	26.3	1.0	0.6	1.6
Education														
< High school graduate	22	9.7	1547	18.8	0.7	0.4	1.1	13	11.1	573	19.1	0.7	0.3	1.3
High school graduate	42	18.4	1974	24.0	Ref			27	23.1	761	26.6	Ref		
> High school graduate	164	71.9	4714	57.2	**1.6**	**1.2**	**2.3**	77	65.8	1524	53.3	1.4	0.9	2.2
Annual household income														
< $10,000	26	11.4	1447	17.6	0.9	0.6	1.4	19	16.2	573	20.0	0.9	0.5	1.6
$10,000–$50,000	113	49.6	2549	30.9	Ref			48	41.0	838	29.3	Ref		
> $50,000	71	31.1	3431	41.6	**2.1**	**1.6**	**2.9**	45	38.5	1234	43.2	1.6	1.0	2.4
Smoking[b]														
Yes	41	18.0	1492	18.1	1.0	0.7	1.4	24	20.5	693	24.2	0.8	0.8	1.3
No	187	82.0	6627	80.4	Ref			92	78.6	2135	74.7	Ref		
Oral contraceptive use[b]														
Yes	15	6.6	614	7.5	0.9	0.5	1.5	10	8.6	221	7.7	1.1	0.6	2.2
No	211	93	7581	92.0	Ref			107	91.5	2621	91.7	Ref		
Folic acid use[b]														
Yes	142	62.3	4132	50.1	**1.6**	**1.2**	**2.1**	76	65.0	1364	47.7	**2.0**	**1.4**	**3.0**

Maternal characteristic	Controls							Isolated Orofacial Clefts						
	Mothers of twins		Mothers of singletons					Mothers of twins		Mothers of singletons				
	n	%	n	%	cOR	LCL	UCL	n	%	n	%	cOR	LCL	UCL
No	86	37.7	4076	49.5	Ref			41	35.0	1486	52.0	Ref		
Study site														
Arkansas	19	8.3	1050	12.7	0.7	0.4	1.2	12	10.3	321	11.2	1.4	0.6	3.3
California	8	3.5	1018	12.4	0.3	0.1	0.6	15	12.8	455	15.9	1.2	0.5	2.8
Georgia	24	10.5	866	10.5	Ref			9	7.7	328	11.5	Ref		
Iowa	36	15.8	899	10.9	1.4	0.9	2.4	9	7.7	308	10.8	1.1	0.4	2.7
Massachusetts	51	22.4	977	11.9	**1.9**	**1.2**	**3.1**	19	16.2	391	13.7	1.7	0.8	4.0
New Jersey	27	11.8	546	6.6	1.8	1.0	3.1	7	6.0	156	5.5	1.6	0.6	4.5
New York	12	5.3	718	8.7	0.6	0.3	1.2	19	16.2	233	8.2	**3.0**	**1.3**	**6.7**
North Carolina	14	6.1	580	7.0	0.9	0.4	1.7	7	6.0	164	5.7	1.6	0.6	4.3
Texas	20	8.8	989	12.0	0.7	0.4	1.3	9	7.7	326	11.4	1.0	0.4	
Utah	17	7.5	599	7.3	1.0	0.5	1.9	11	9.4	177	6.2	2.3	0.9	
Year of estimated date of delivery														
1997	2	0.9	103	1.3	*c*			0	0.0	38	1.3	*c*		
1998	29	12.7	733	8.9	1.8	1.0	3.4	13	11.1	266	9.3	1.0	0.5	
1999	22	9.7	842	10.2	1.2	0.6	2.3	16	13.7	327	11.4	1.0	0.5	
2000	26	11.4	871	10.6	1.4	0.7	2.6	13	11.1	291	10.2	0.9	0.4	
2001	22	9.7	775	9.4	1.3	0.3	2.5	14	12.0	285	10.0	1.0	0.5	
2002	22	9.7	683	8.3	1.5	0.8	2.8	10	8.6	246	8.6	0.8	0.4	
2003	20	8.8	875	10.6	1.1	0.6	2.0	6	5.1	222	7.8	0.6	0.2	
2004	19	8.3	890	10.8	1.0	0.5	1.9	8	6.8	299	10.5	0.6	0.3	
2005	26	11.4	835	10.1	1.5	0.8	2.7	12	10.3	305	10.7	0.8	0.4	
2006	23	10.1	841	10.2	1.3	0.7	2.4	11	9.4	289	10.0	0.8	0.4	
2007	17	7.5	792	9.6	Ref			14	12.0	290	10.1	Ref		

Notes. Results in bold indicate statistical significance at $p < 0.05$; cOR = crude odds ratio; LCL=lower 95% confidence limit; UCL=upper 95% confidence limit; Ref= referent category

[a]Percentages may not sum to 100 due to missing values

[b]Any reported use 1 month prior to pregnancy through one month after conception

[c]Not calculated for cell size < 4

Table 2

Twinning among mothers of live-born infants (controls) without major birth defects, by unassisted conception vs. fertility treatment use, National Birth Defects Prevention Study, 1997–2007

	Unassisted Conception												Fertility Treatment Use						
	Mothers of twins		Mothers of singletons										Mothers of twins		Mothers of singletons				
Maternal characteristic	n	%	n	%	cOR	LCL	UCL	aOR	LCL	UCL	n	%	n	%	cOR	LCL	UCL
N	155		7906								71		249				
Age at delivery (years)																	
<25	39	25.2	2767	35.0	0.7	0.4	1.0	0.7	0.5	1.2	0	0.0	18	7.2*	*b*		
25–29	46	29.7	2188	27.7	Ref			Ref[a]			8	11.3	54	21.7	Ref		
30–34	39	25.2	1920	24.3	1.0	0.6	1.5	1.0	0.6	1.6	39	54.9	98	39.4	**2.7**	**1.2**	**6.2**
≥35	31	20.0	1031	13.0	1.4	0.9	2.3	1.4	0.9	2.3	24	33.8	79	31.7	2.1	0.9	4.9
Race/ethnicity																	
Non-Hispanic white	91	58.7	4561	57.7	Ref			Ref[c]			65	91.6	209	83.9	Ref		
Non-Hispanic black	29	18.7	906	11.5	**1.6**	**1.1**	**2.5**	**1.6**	**1.0**	**2.4**	2	2.8	11	4.4	*b*		
Hispanic	25	16.1	1909	24.2	0.7	0.4	1.0	0.7	0.4	1.0	2	2.8	18	7.3	*b*		
Other	10	6.5	521	6.6	1.0	0.5	1.9	1.0	0.5	1.8	2	2.8	11	4.4	*b*		
Height (cm)																	
<159	35	22.6	2020	25.6	Ref			Ref[d]			17	23.9	44	17.8	Ref		
159–163	47	30.3	2007	25.4	1.4	0.9	2.2	1.3	0.9	2.1	9	12.7	62	24.9	**0.4**	**0.2**	**0.9**
164–170	34	21.9	1802	22.8	1.1	0.7	1.8	1.1	0.7	1.8	19	26.8	61	24.5	0.8	0.4	1.7
>170	35	22.6	1783	22.6	1.2	0.7	1.9	1.1	0.7	1.8	26	36.6	80	32.1	0.8	0.4	1.7
Pre-pregnancy weight (kg)																	
<57	34	21.9	2009	25.4	Ref			Ref[e]			12	16.9	40	16.1	Ref		
57–64	37	23.9	2241	28.4	1.0	0.6	1.6	0.9	0.6	1.6	19	26.8	64	25.7	1.2	0.4	2.3
65–75	43	27.7	1806	22.8	1.4	0.9	2.2	1.4	0.9	2.3	23	32.4	55	22.1	1.4	0.6	3.1
>75	36	23.2	1771	22.4	1.2	0.7	1.9	1.2	0.7	2.0	17	23.9	90	36.1	0.6	0.3	1.4
Pre-pregnancy body mass index (kg/m^2)																	
Underweight (<18.5)	7	4.5	419	5.3	0.9	0.4	2.0	1.1	0.5	2.4	2	4.1	5	2.0	1.3	0.2	6.9

Maternal characteristic	Unassisted Conception: Mothers of twins n	%	Mothers of singletons n	%	cOR	LCL	UCL	aOR	LCL	UCL	Fertility Treatment Use: Mothers of twins n	%	Mothers of singletons n	%	cOR	LCL	UCL
Normal (18.5–24.9)	78	50.3	4188	53.0	Ref			Ref[f]			38	53.5	123	49.4	Ref		
Overweight (25–29.9)	34	21.9	1720	21.8	1.1	0.7	1.6	1.1	0.7	1.7	21	29.6	61	24.5	1.1	0.6	2.1
Obese (≥ 30)	28	18.1	1245	15.8	1.2	0.7	1.8	1.2	0.8	2.0	10	14.1	58	23.3	0.6	0.3	1.2
Parity																	
0	47	30.3	3114	39.4	Ref			Ref[g]			46	64.8	142	57.0	Ref		
1	55	35.5	2629	33.3	1.4	1.0	2.1	1.4	0.9	2.1	19	26.8	75	30.1	0.8	0.4	1.4
2+	53	34.2	2162	27.4	**1.7**	**1.1**	**2.5**	1.6	1.0	2.5	6	8.5	32	12.9	0.6	0.2	1.5
Education																	
< High school graduate	21	13.6	1509	19.1	0.7	0.4	1.2	0.8	0.4	1.3	1	1.4	8	3.2	*b*		
High school graduate	38	24.5	1929	24.4	Ref			Ref[h]			4	5.6	31	12.5	Ref		
> High school graduate	96	61.9	4461	56.4	1.1	0.7	1.6	1.0	0.6	1.4	66	93.0	210	84.3	2.4	0.8	7.2
Annual household income																	
< $10,000	25	16.1	1429	18.1	0.9	0.6	1.5	1.1	0.7	1.8	1	1.4	14	5.6	*b*		
$10,000–$50,000	64	41.3	3332	42.2	Ref			Ref[i]			7	9.9	148	59.4	Ref		
> $50,000	54	34.8	2374	30.0	1.2	0.8	1.7	1.0	0.7	1.5	58	81.7	77	30.9	**4.3**	**1.9**	**9.9**
Smoking[j]																	
Yes	38	24.5	1464	18.5	1.4	1.0	2.0	**1.6**	**1.1**	**2.4**	3	4.2	19	7.6	*b*		
No	117	75.5	6345	80.3	Ref			Ref[f]			68	95.8	229	92.0	Ref		
Oral contraceptive use[j]																	
Yes	10	6.5	603	7.6	0.8	0.4	1.6	0.8	0.4	1.6	5	7.0	7	2.8	2.6	0.8	8.5
No	144	92.9	7278	92.1	Ref			Ref[g]			66	93.0	242	97.2	Ref		
Folic acid use[j]																	
Yes	73	47.1	3874	49.0	0.9	0.7	1.3	0.8	0.6	1.2	67	94.4	217	87.2	2.5	0.8	7.2
No	82	52.9	4016	50.8	Ref			Ref[f]			4	5.6	32	12.9	Ref		
Study site																	
Arkansas	16	10.3	1005	12.7	0.7	0.4	1.5	0.8	0.4	1.5	3	4.2	33	13.3	*b*		
California	8	5.2	996	12.6	**0.4**	**0.2**	**0.9**	**0.4**	**0.2**	**0.9**	0	0.0	11	4.4	*b*		

Maternal characteristic	Unassisted Conception										Fertility Treatment Use						
	Mothers of twins		Mothers of singletons								Mothers of twins		Mothers of singletons				
	n	%	n	%	cOR	LCL	UCL	aOR	LCL	UCL	n	%	n	%	cOR	LCL	UCL
Georgia	18	11.6	835	10.6	Ref			Ref[k]			6	8.5	22	8.5	Ref		
Iowa	24	15.5	845	10.7	1.3	0.7	2.4	1.3	0.7	2.5	12	16.9	43	17.3	1.0	0.3	3.1
Massachusetts	21	13.6	921	11.7	1.1	0.6	2.0	1.1	0.6	2.0	30	42.3	52	20.9	2.1	0.8	5.8
New Jersey	16	10.3	531	6.7	1.4	0.7	2.8	1.2	0.6	2.4	11	15.5	10	4.0	4.0	1.2	14.0
New York	9	5.8	690	8.7	0.6	0.3	1.4	0.6	0.3	1.3	2	2.8	20	8.0	*b*		
North Carolina	12	7.7	555	8.0	1.0	0.5	2.1	1.3	0.6	2.8	2	2.8	17	6.8	*b*		
Texas	19	12.3	958	12.1	0.9	0.5	1.8	0.9	0.5	1.8	1	1.4	18	7.2	*b*		
Utah	12	7.7	570	7.2	1.0	0.5	2.0	1.2	0.6	2.7	4	5.6	23	9.2	0.6	0.2	2.6
Year of estimated date of delivery																	
1997	1	0.7	96	1.2	*b*			*b*			1	1.4	1	0.4	*b*		
1998	19	12.3	705	8.9	1.7	0.8	3.6	1.9	0.9	4.0	9	12.7	19	7.7	2.3	0.7	7.9
1999	17	11.0	800	10.1	1.4	0.6	2.9	1.5	0.7	3.2	5	7.0	30	12.1	0.8	0.2	3.1
2000	17	11.0	837	10.6	1.3	0.6	2.8	1.4	0.7	3.2	9	12.7	26	10.4	1.7	0.5	5.7
2001	17	11.0	748	9.5	1.4	0.7	3.1	1.6	0.7	3.5	5	7.0	19	7.6	1.3	0.3	5.0
2002	15	9.7	666	8.4	1.4	0.7	3.1	1.6	0.7	3.6	7	9.9	14	5.6	2.4	0.6	9.0
2003	13	8.4	836	10.6	1.0	0.5	2.2	1.0	0.4	2.1	7	9.9	31	12.5	1.1	0.3	3.8
2004	11	7.1	843	10.7	0.8	0.4	1.9	0.9	0.4	1.9	7	9.9	33	13.3	1.0	0.3	3.6
2005	18	11.6	793	10.0	1.4	0.7	3.0	1.5	0.7	3.1	8	11.3	31	12.5	1.2	0.4	4.3
2006	15	9.7	815	10.3	1.2	0.5	2.5	1.2	0.6	2.6	8	11.3	21	8.4	1.8	0.5	6.5
2007	12	7.7	765	9.7	Ref			Ref[k]			5	7.0	24	9.6	Ref		

Notes. Results in bold indicate statistical significance at $p < 0.05$; cOR = crude odds ratio; aOR= adjusted odds ratio; LCL =lower 95% confidence limit; UCL=upper 95% confidence limit; Ref=referent category

[*] Percentages may not sum to 100 due to missing values

[a] Adjusted for maternal race/ethnicity, education level, annual household income, study site, year of expected date of delivery (EDD)

[b] OR not calculated for cell size < 4

[c] Adjusted for study site

[d] Adjusted for year of mother's birth, maternal race/ethnicity, study site

[e] Adjusted for maternal age, race/ethnicity, height, education level, annual household income, parity, study site, year of EDD

[f] Adjusted for maternal age, race/ethnicity, education level, annual household income, parity, study site, year of EDD

[g] Adjusted for maternal age, race/ethnicity, education level, annual household income, study site

[h] Adjusted for maternal age, race/ethnicity, study site, year of EDD

[i] Adjusted for maternal age, race/ethnicity, education level, study site, year of EDD

[j] Any reported use one month prior to pregnancy through one month after conception

[k] Model included study site and year of EDD

Table 3

Twinning among mothers of infants or fetuses with isolated orofacial clefts, by unassisted conception vs. fertility treatment use, National Birth Defects Prevention Study, 1997–2007

	Unassisted Conception												Fertility Treatment Use						
	Mothers of twins		Mothers of singletons										Mothers of twins		Mothers of singletons				
Maternal characteristic	**n**	**%**	**n**	**%**	**cOR**	**LCL**	**UCL**	**aOR**	**LCL**	**UCL**	**n**	**%**	**n**	**%**	**cOR**	**LCL**	**UCL**
N	82		2706								35		121				
Age at delivery (years)																	
<25	26	31.7	974	36.0	0.8	0.4	1.4	0.7	0.4	1.3	1	2.9	9	7.4	*b*		
25–29	25	30.5	730	27.0	Ref			Ref[a]			6	17.1	35	28.9	Ref		
30–34	21	25.6	617	22.8	1.0	0.6	1.8	1.0	0.6	1.9	14	40.0	40	33.1	2.0	0.7	5.9
≥35	10	12.2	385	14.2	0.8	0.4	1.6	0.8	0.4	1.6	14	40.0	37	30.6	2.2	0.8	6.4
Race/ethnicity																	
Non-Hispanic white	46	56.1	1681	62.1*	Ref			Ref[c]			32	91.4	100	82.6	Ref		
Non-Hispanic black	10	12.2	166	6.1	**2.2**	**1.1**	**4.4**	**2.3**	**1.1**	**4.6**	0	0.0	2	1.7	*b*		
Hispanic	21	25.6	664	24.5	1.2	0.7	2.0	1.2	0.7	2.0	1	2.9	10	8.3	*b*		
Other	5	6.1	194	7.2	0.9	0.4	2.4	0.9	0.4	2.4	2	5.7	9	7.4	*b*		
Height (cm)																	
<159	17	20.7	721	26.6	Ref			Ref[d]			6	17.1	28	23.1	Ref		
159–163	20	24.4	640	23.7	1.3	0.7	2.6	1.4	0.7	2.6	10	28.6	30	24.8	1.6	0.5	4.8
164–170	13	15.9	607	22.4	0.9	0.4	1.9	1.0	0.5	2.0	10	28.6	30	24.8	1.6	0.5	4.8
>170	27	32.9	633	23.4	1.8	1.0	3.4	1.9	0.9	1.4	9	23.7	29	24.0	1.4	0.5	4.6
Pre-pregnancy weight (kg)																	
<57	14	17.1	692	25.6	Ref			Ref[e]			8	22.9	23	19.0	Ref		
57–64	19	23.2	725	26.8	1.3	0.6	2.6	1.0	0.5	2.0	12	34.3	29	24.0	1.2	0.4	3.4
65–75	20	24.4	611	22.6	1.6	0.8	3.2	1.3	0.6	2.7	7	20.0	25	20.7	0.8	0.3	2.6
>75	28	34.2	646	23.9	2.1	1.1	4.1	1.6	0.8	3.2	8	22.9	42	34.7	0.5	0.2	1.7
Pre-pregnancy body mass index (kg/m^2)																	
Underweight (<18.5)	6	7.3	181	6.7	1.4	0.6	3.3	1.5	0.6	3.6	2	5.7	2	1.7	*b*		

	Unassisted Conception												Fertility Treatment Use						
	Mothers of twins		Mothers of singletons										Mothers of twins		Mothers of singletons				
Maternal characteristic	n	%	n	%	cOR	LCL	UCL	aOR	LCL	UCL			n	%	n	%	cOR	LCL	UCL
Normal (18.5–24.9)	33	40.2	1370	50.6	Ref			Ref[f]					22	62.9	58	47.9	Ref		
Overweight (25–29.9)	19	23.2	564	20.8	1.4	0.8	2.5	1.2	0.6	2.2			5	3.1	26	21.5	0.5	0.2	1.5
Obese (≥ 30)	19	23.2	470	17.4	1.7	0.9	3.0	1.6	0.9	2.9			6	17.1	31	25.6	0.5	0.2	1.4
Parity																			
0	26	31.7	1036	38.3	Ref			Ref[g]					22	62.9	72	59.5	Ref		
1	28	34.2	932	34.4	1.2	0.7	2.1	1.3	0.7	2.3			9	25.7	37	30.6	0.8	0.3	1.9
2+	28	34.2	737	27.2	1.5	0.9	2.6	1.7	0.9	3.1			4	11.4	12	9.9	1.1	0.3	3.7
Education																			
< High school graduate	13	15.9	556	20.6	0.7	0.4	1.4	0.7	0.3	1.3			0	0.0	7	5.8	*b*		
High school graduate	25	30.5	740	27.4	Ref			Ref[h]					2	5.7	13	10.7	Ref		
> High school graduate	44	53.7	1410	52.1	0.9	0.6	1.5	1.0	0.6	1.6			33	94.3	100	82.6	*b*		
Annual household income																			
< $10,000	18	22.0	564	20.8	1.1	0.6	1.9	1.2	0.6	2.1			1	2.9	9	7.4	*b*		
$10,000–$50,000	36	43.9	1190	44.0	Ref			Ref[i]					9	25.7	33	27.3	Ref		
> $50,000	23	28.1	752	27.8	1.0	0.6	1.7	0.9	0.5	1.7			25	71.4	77	63.6	1.2	0.5	2.8
Smoking[j]																			
Yes	18	22.0	676	25.0	0.8	0.5	1.4	0.9	0.5	1.5			6	17.1	9	7.4	2.6	0.8	7.8
No	63	76.8	2008	74.2	Ref			Ref[f]					29	82.9	112	92.6	Ref		
Oral contraceptive use[j]																			
Yes	8	9.8	218	8.1	1.2	0.6	2.6	1.2	0.5	2.6			2	5.7	2	1.7	*b*		
No	74	90.2	2480	91.7	Ref			Ref[g]					33	94.3	119	98.4	Ref		
Folic acid use[j]																			
Yes	42	51.2	1246	46.1	1.2	0.8	1.9	1.2	0.8	2.0			34	97.1	100	82.6	*b*		
No	40	48.8	1457	53.8	Ref			Ref[f]					1	2.9	21	17.4	Ref		
Study site																			
Arkansas	10	12.2	307	11.4	1.4	0.5	3.8	1.4	0.5	3.8			2	5.7	10	8.3	*b*		
California	14	17.1	435	16.1	1.4	0.6	3.5	1.4	0.6	3.5			1	2.9	13	10.7	*b*		

	Unassisted Conception												Fertility Treatment Use						
	Mothers of twins		Mothers of singletons										Mothers of twins		Mothers of singletons				
Maternal characteristic	**n**	**%**	**n**	**%**	**cOR**	**LCL**	**UCL**	**aOR**	**LCL**	**UCL**			**n**	**%**	**n**	**%**	**cOR**	**LCL**	**UCL**
Georgia	7	8.5	303	11.2	Ref			Ref[k]					2	5.7	22	18.2	Ref		
Iowa	9	11.0	290	10.7	1.3	0.5	3.7	1.4	0.5	3.7			0	0.0	13	10.7	*b*		
Massachusetts	9	11.0	357	13.2	1.1	0.4	3.0	1.1	0.4	3.0			10	28.6	29	24.0	*b*		
New Jersey	2	2.4	150	5.5	*b*			*b*					5	14.3	5	4.1	*b*		
New York	14	17.1	223	8.2	**2.7**	**1.1**	**6.8**	2.5	1.0	6.3			5	14.3	8	6.6	*b*		
North Carolina	3	7.3	158	5.8	*b*			*b*					4	11.4	5	4.1	*b*		
Texas	8	9.8	315	11.6	1.1	0.4	3.1	1.0	0.4	2.9			1	2.9	7	5.8	*b*		
Utah	6	7.3	168	6.2	1.5	0.5	4.7	1.8	0.6	5.7			5	14.3	9	7.4	*b*		
Year of estimated date of delivery																			
1997	0	0.0	36	1.3	b			*b*					0	0.0	0	0.0	*b*		
1998	9	11.0	253	9.4	1.4	0.5	3.9	1.6	0.6	4.5			4	11.4	9	7.4	0.5	0.1	2.4
1999	8	9.8	308	11.4	1.0	0.4	2.9	1.1	0.4	3.3			8	22.9	16	13.2	0.6	0.2	2.1
2000	11	13.4	278	10.3	1.6	0.6	4.1	1.6	0.6	4.5			2	5.7	7	5.8	*b*		
2001	12	14.6	271	10.0	1.8	0.7	4.6	1.9	0.7	5.0			2	5.7	12	9.9	*b*		
2002	7	8.5	235	8.7	1.2	0.4	3.4	1.2	0.4	3.7			3	8.6	7	5.8	*b*		
2003	4	4.9	202	7.5	0.8	0.2	2.7	0.9	0.2	3.1			2	5.7	16	13.2	*b*		
2004	7	8.5	281	10.4	1.0	0.3	2.9	1.0	0.3	2.9			1	2.9	16	13.2	*b*		
2005	10	12.2	289	10.7	1.4	0.5	3.7	1.3	0.5	3.6			2	5.7	13	10.7	*b*		
2006	7	8.5	272	10.1	1.0	0.4	3.0	1.0	0.3	2.9			4	11.4	17	14.1	0.3	0.1	1.2
2007	7	8.5	280	10.4	Ref			Ref[k]					7	20.0	8	6.6	Ref		

Notes. Results in bold indicate statistical significance at $p < 0.05$; cOR = crude odds ratio; aOR= adjusted odds ratio; LCL =lower 95% confidence limit; UCL=upper 95% confidence limit; Ref=referent category

[*] Percentages may not sum to 100 due to missing values

[a] Adjusted for maternal race/ethnicity, education level, annual household income, study site, year of expected date of delivery (EDD)

[b] OR not calculated for cell size < 4

[c] Adjusted for study site

[d] Adjusted for year of mother's birth, maternal race/ethnicity, study site

[e] Adjusted for maternal age, race/ethnicity, height, education level, annual household income, parity, study site, year of EDD

[f] Adjusted for maternal age, race/ethnicity, education level, annual household income, parity, study site, year of EDD

[g] Adjusted for maternal age, race/ethnicity, education level, annual household income, study site

[h] Adjusted for maternal age, race/ethnicity, study site, year of EDD

[i] Adjusted for maternal age, race/ethnicity, education level, study site, year of EDD

[j] Any reported use one month prior to pregnancy through one month after conception

[k] Model included study site and year of EDD

Table 4

Twinning among mothers of live-born infants without major birth defects, by estimated zygosity, National Birth Defects Prevention Study, 1997–2007

	Unlike-sex twins				Dizygotic twins (estimated)			Like-sex twins				Monozygotic twins (estimated)		
Maternal characteristic	**n**	**cOR**	**LCL**	**UCL**	**cOR**	**LUI**	**UUI**	**n**	**cOR**	**LCL**	**UCL**	**cOR**	**LUI**	**UUI**
Fertility treatment use (any)														
Yes	29	**26.5**	**16.0**	**44.3**	**14.7**	**12.6**	**16.9**	30	**11.7**	**7.6**	**18.2**	**9.6**	**5.4**	**14.7**
No	35	Ref			Ref			82	Ref			Ref		
Assisted reproductive technology use														
Yes	16	**84.6**	**43.3**	**165.3**	**59.7**	**49.1**	**71.2**	17	**38.4**	**20.9**	**70.6**	**40.1**	**17.7**	**66.2**
No	35	Ref			Ref			82	Ref			Ref		
Clomiphene citrate use														
Yes	8	**14.9**	**6.7**	**32.8**	**10.2**	**7.8**	**12.9**	8	**6.3**	**3**	**13.4**	**6.6**	**1.7**	**12.4**
No	35	Ref			Ref			82	Ref			Ref		
Age at delivery (years)[a]														
<25	8	0.9	0.3	2.4	**0.7**	**0.5**	**0.9**	18	0.6	0.3	1.1	0.6	0.3	1.2
25–29	7	Ref			Ref			24	Ref			Ref		
30–34	11	1.7	0.7	4.4	1.3	0.9	1.7	22	1.0	0.6	1.8	1.1	0.5	2.0
≥35	9	**2.6**	**1.0**	**7.0**	**1.9**	**1.3**	**2.6**	18	1.5	0.8	2.8	1.6	0.7	3.2
Race/ethnicity[a]														
Non-Hispanic white	24	Ref			Ref			48	Ref			Ref		
Non-Hispanic black	7	1.3	0.6	3.1	**1.5**	**1.0**	**1.9**	17	1.6	0.9	2.8	1.7	0.7	3.0
Hispanic	4	0.4	0.1	1.1	**0.4**	**0.3**	**0.6**	11	**0.5**	**0.3**	**1.0**	**0.5**	**0.2**	**1.0**
Other	0	*b*			**0.6**	**0.2**	**1.0**	6	1.1	0.5	2.5	1.1	0.0	2.4
Height (cm)[a]														
<159	7	Ref			Ref			15	Ref			Ref		
159–163	12	1.8	0.7	4.5	1.7	1.3	2.3	24	1.6	0.9	3.1	1.8	0.8	4.1
164–170	7	1.2	0.4	3.3	1.4	1.0	2.0	20	1.6	0.8	3.1	1.8	0.7	4.0
>170	9	1.5	0.6	4.1	**1.6**	**1.1**	**2.3**	21	1.7	0.9	3.2	1.9	0.7	4.4
Pre-pregnancy weight (kg)[a]														
<57	5	Ref			Ref			18	Ref			Ref		
57–64	8	1.4	0.5	4.4	1.3	0.9	1.8	23	1.2	0.6	2.1	1.3	0.5	2.7

	Unlike-sex twins				Dizygotic twins (estimated)			Like-sex twins				Monozygotic twins (estimated)		
Maternal characteristic	**n**	**cOR**	**LCL**	**UCL**	**cOR**	**LUI**	**UUI**	**n**	**cOR**	**LCL**	**UCL**	**cOR**	**LUI**	**UUI**
65–75	9	2.0	0.7	6.1	**1.7**	**1.1**	**2.4**	23	1.4	0.8	2.7	1.6	0.6	3.4
>75	11	2.5	0.9	7.1	**1.6**	**1.1**	**2.3**	17	1.1	0.5	2.1	1.2	0.5	2.5
Pre-pregnancy body mass index (kg/m^2)[a]														
Underweight (<18.5)	1	*b*			**0.6**	**0.2**	**1.0**	3	*b*			1.0	0.4	1.9
Normal (18.5–24.9)	18	Ref			Ref			43	Ref			Ref		
Overweight (25–29.9)	6	0.8	0.3	2.0	1.0	0.7	1.3	20	1.1	0.6	1.8	1.2	0.5	2.2
Obese (≥ 30)	8	1.5	0.6	3.4	1.2	0.9	1.5	13	1.0	0.5	1.8	1.0	0.4	1.9
Parity[a]														
0	9	Ref			Ref			28	Ref			Ref		
1	14	1.9	0.9	4.8	**1.4**	**1.1**	**1.9**	28	1.2	0.7	2.0	1.3	0.6	2.4
2+	12	2.0	0.9	4.8	**1.6**	**1.2**	**2.2**	26	1.4	0.8	2.4	1.5	0.7	2.8
Education[a]														
< High school graduate	4	0.6	0.2	1.9	**0.6**	**0.4**	**0.9**	11	0.7	0.3	1.5	0.7	0.2	1.4
High school graduate	9	Ref			Ref			21	Ref			Ref		
> High school graduate	22	1.1	0.5	2.4	1.1	0.9	1.4	50	1.1	0.6	1.8	1.1	0.6	2.1
Annual household income[a]														
< $10,000	6	1.7	0.6	4.8	1.1	0.8	1.5	14	0.9	0.5	1.6	0.9	0.4	1.8
$10,000–$50,000	16	Ref			Ref			29	Ref			Ref		
> $50,000	8	**2.8**	**1.2**	**6.4**	**1.6**	**1.2**	**2.1**	35	1.1	0.7	1.9	1.2	0.6	2.1
Smoking[a,c]														
Yes	28	1.0	0.5	2.4	1.2	0.9	1.5	62	1.3	0.8	2.2	1.4	0.7	2.3
No	7	Ref			Ref			20	Ref			Ref		
Oral contraceptive use[a,c]														
Yes	1	*b*			0.9	0.5	1.3	8	1.3	0.6	2.7	1.3	0.3	2.5
No	34	Ref			Ref			73	Ref			Ref		
Folic acid use[a,c]														
Yes	20	1.5	0.7	2.8	1.0	0.8	1.3	34	0.8	0.5	1.2	0.8	0.4	1.3
No	15	Ref			Ref			48	Ref			Ref		

Notes. Comparison group for all analyses was mothers of singleton controls. Results in bold indicate statistical significance at $p < 0.05$; cOR = crude odds ratio; LCL =lower 95% confidence limit; UCL=upper 95% confidence limit; LUI= lower 95% uncertainty interval value; UUI= upper 95% uncertainty interval value; Ref=referent category

[a]Analysis restricted to mothers who reported unassisted conception

[b]OR not calculated for cell size ≤2

[c]Any reported use 1 month prior to pregnancy through one month after conception